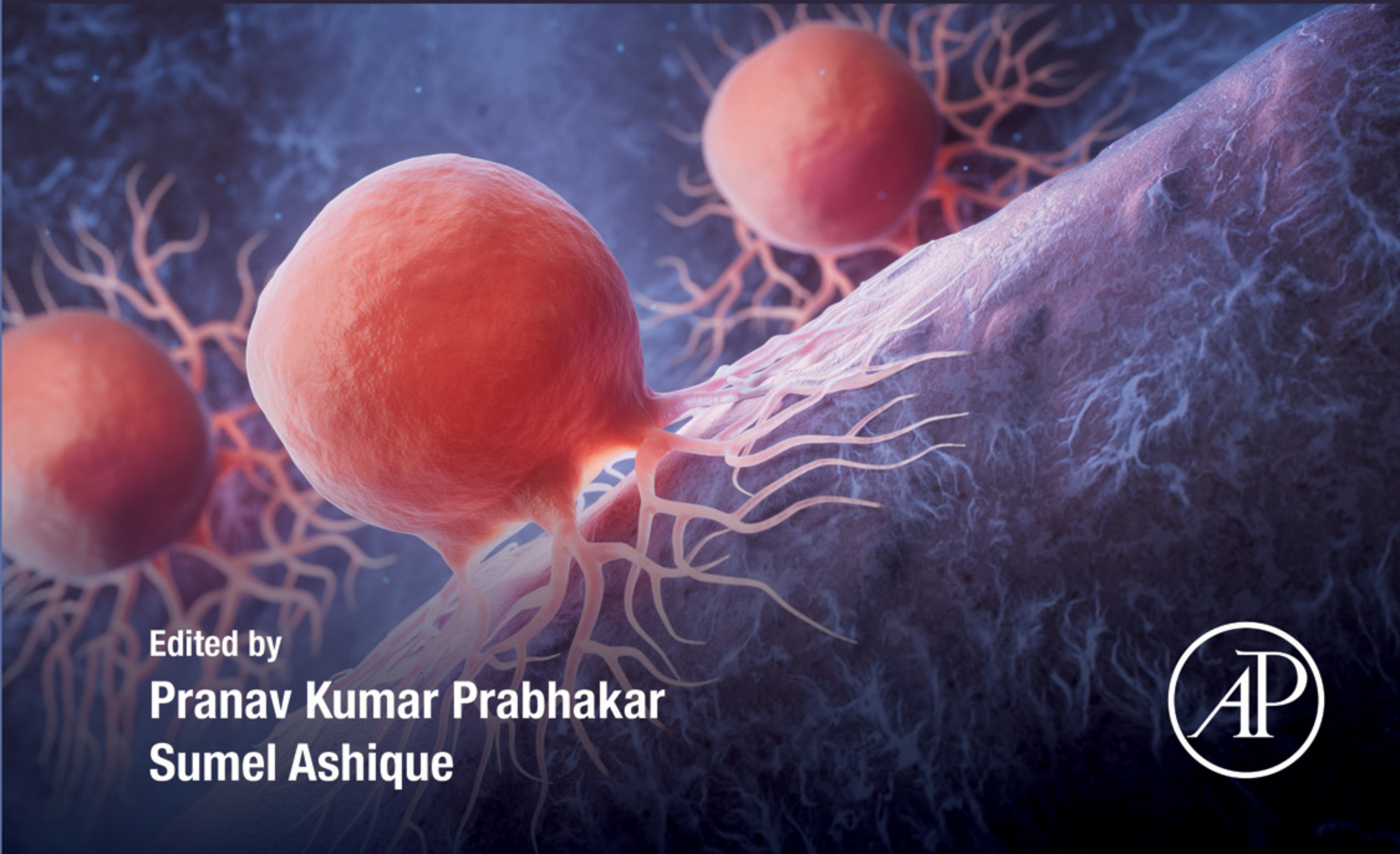
Unlocking Sirtuins

Cellular Biology to Translational Research



Edited by

Pranav Kumar Prabhakar
Sumel Ashique

Unlocking Sirtuins

This page intentionally left blank

Unlocking Sirtuins

Cellular Biology to Translational Research

Edited by

Pranav Kumar Prabhakar
Department of Biotechnology, School of Engineering and Technology,
Nagaland University, Meriema, Kohima, Nagaland, India

Sumel Ashique
Department of Pharmaceutical Technology, Bharat Technology,
Uluberia, West Bengal, India

ELSEVIER
ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Copyright © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

For accessibility purposes, images in electronic versions of this book are accompanied by alt text descriptions provided by Elsevier. For more information, see https://www.elsevier.com/about/accessibility.

Books and Journals published by Elsevier comply with applicable product safety requirements. For any product safety concerns or queries, please contact our authorised representative, Elsevier B.V., at productsafety@elsevier.com.

Publisher's note: Elsevier takes a neutral position with respect to territorial disputes or jurisdictional claims in its published content, including in maps and institutional affiliations.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-443-45380-9

For Information on all Academic Press publications
visit our website at https://www.elsevier.com/books-and-journals

Publisher: Megan Ball
Acquisitions Editor: Michelle Fisher
Editorial Project Manager: Ashavari Bhattacharya
Production Project Manager: Sathyavani Deivasigamani
Cover Designer: Venkatraman Gopalakrishan

Typeset by MPS Limited, Chennai, India

ELSEVIER
Book Aid International
Working together
to grow libraries in
developing countries
www.elsevier.com • www.bookaid.org

Contents

List of contributors xv
Preface xix

Part 1 Introduction to sirtuins

1. Sirtuin proteins: structure, functions, and evolutionary insights 3
Neetu Sachan, Prakhar Varshney, Phool Chandra and Pradeep Singh
  1.1 Introduction 3
  1.2 Historical perspective: from silent information regulator 2 to human sirtuins 4
  1.3 Structural biology of sirtuins 6
  1.4 Classification and subcellular localization 7
  1.5 Tissue-specific sirtuin expression and function 9
  1.6 Physiological functions 13
  1.7 Sirtuins in health and disease 15
  1.8 Sex and age-related differences in sirtuin function 17
  1.9 Evolutionary insights 22
  1.10 Biomarkers to track sirtuin-targeted therapy efficacy 23
  1.11 Environmental and lifestyle influences on sirtuins 26
  1.12 Translational applications 29
  1.13 Future perspectives and challenges 30
  1.14 Conclusion 31
  References 33

2. Nicotinamide adenine dinucleotide-dependent enzymatic mechanisms and nicotinamide adenine dinucleotide precursors (nicotinamide mononucleotide, nicotinamide riboside) 43

Zahid Ahmad Thoker, Lovleen Marwaha and Ajit Prakash

2.1 Introduction 43
2.2 Chemistry and biosynthesis of nicotinamide adenine dinucleotide 46
2.3 Nicotinamide adenine dinucleotide-dependent enzymatic systems 50
2.4 Physiological and molecular significance of nicotinamide adenine dinucleotide 51
2.5 Nicotinamide adenine dinucleotide precursors: nicotinamide mononucleotide and nicotinamide riboside 52
2.6 Therapeutic potential and translational evidence 53
2.7 Analytical and experimental methods 55
2.8 Challenges and unresolved questions 56
2.9 Future directions and perspectives 58
2.10 Conclusions 60
References 60

Part 2 Sirtuins and aging

3. Sirtuins in senescence, mitochondrial health, and longevity 65

Sanjib Manna, Purabi Das and Subhajit Mandal

3.1 Introduction 65
3.2 Sirtuins in cellular senescence 67
3.3 Sirtuins and mitochondrial health 72
3.4 Sirtuins and longevity 84
3.5 Therapeutic implications and future directions 87
3.6 Conclusion 89
References 90

4. DNA repair and genome maintenance via sirtuin pathways 99

Samarendra Singh, Farhan Raza, Aditya Raj, Gautam Singh and Navjot Kaur Sandhu

4.1 Introduction 99
4.2 Sirtuins in DNA repair pathways 104
4.3 Chromatin dynamics and DNA damage response 113
4.4 Nicotinamide adenine dinucleotide availability and metabolic regulation 118
4.5 Pathological implications of sirtuin dysfunction 121
4.6 Therapeutic potential of targeting sirtuins 125
4.7 Future perspectives 129
4.8 Conclusion 131
References 132

Part 3 Sirtuins in metabolic regulation

5. Sirtuins and energy homeostasis 141

Bhupender Nehra, Rishabh Kasnia, Sunaina Demiwal, Sourabh Suthar and Biplab Debnath

5.1 Introduction 141
5.2 Molecular mechanisms linked to sirtuin action 145
5.3 Sirtuins and cellular energy homeostasis 147
5.4 Tissue-specific roles of sirtuins in metabolic regulation 150
5.5 Sirtuins and nutrient sensing pathways 154
5.6 Sirtuins in metabolic disorders 155
5.7 Sirtuins and cellular stress responses 158
5.8 Pharmacological modulation of sirtuins 160
5.9 Sirtuins, aging, and longevity 165
5.10 Emerging insights and omics approaches 168
5.11 Therapeutic implications and translational perspectives 169
5.12 Future directions 171

5.13 Conclusions 171
References 172

6. Role of sirtuins in glucose and lipid metabolism 183

Verma Swastik and Kotnis Ashwin

6.1 Introduction 183
6.2 Overview of sirtuins 184
6.3 Nicotinamide adenine dinucleotide metabolism and mechanism of action 186
6.4 Regulation of sirtuin expression and activity 188
6.5 Carbohydrate-specific roles 190
6.6 Lipid-specific roles of sirtuins 192
6.7 Integrated carbohydrate–lipid regulation 194
6.8 Sirtuins in disease and physiology 197
6.9 Therapeutic targeting 199
6.10 Experimental approaches and methods 202
6.11 Conclusions and future directions 205
References 205

7. Sirtuins in caloric restriction and fasting responses 215

Rizwan Ahamad, Nazreen Tabassum, Nasr Ali Emad, Mohd Aqil and Mohd Mujeeb

7.1 Introduction 215
7.2 Classification and functions of sirtuins 216
7.3 Roles of SIRT1 218
7.4 Modulation of SIRT1 219
7.5 Other members of the sirtuins family 220
7.6 Adenosine monophosphate-activated protein kinase 222
7.7 Sirtuin activation in caloric restriction and fasting 224
7.8 Functional roles in metabolic adaptation 227
7.9 Sirtuins in aging and disease prevention 235

7.10 Therapeutic potential and future perspectives 238
References 239

Part 4 Sirtuins in disease pathology

8. **Sirtuins in neurodegenerative diseases** **249**
Neetu Sachan, Zeeshan Ali, Nishat Fatma and Phool Chandra
8.1 Introduction 249
8.2 Functional roles of individual sirtuins 251
8.3 Mechanisms of sirtuin action in the nervous system 254
8.4 Sirtuins in major neurodegenerative diseases 262
8.5 Pharmacological activators 268
8.6 Sirtuin inhibitors and dual modulators 269
8.7 Experimental and clinical evidence 274
8.8 Clinical and translational perspectives 276
8.9 Translational challenges and limitations 279
8.10 Conclusion 280
References 281

9. **Sirtuins in cardiovascular health** **291**
Anas Islam, Badruddeen, Mohammad Irfan Khan, Juber Akhtar and Asad Ahmad
9.1 Introduction 291
9.2 Expression and localization of sirtuins in cardiovascular tissues 293
9.3 Mechanistic roles of sirtuins in cardiovascular physiology 297
9.4 Sirtuins in specific cardiovascular diseases 300
9.5 Sirtuin modulators: therapeutic potential in cardiovascular disease 304
9.6 Sirtuins and cardiometabolic syndrome 309
9.7 Crosstalk with other cardioprotective pathways 312

9.8 Challenges and future directions 316
9.9 Conclusion 318
AI disclosure 319
References 319

10. The role of sirtuins in cancer progression 331
Anas Islam, Usama Ahmad, Mohd Muazzam Khan and Talib Hussain
10.1 Introduction 331
10.2 Mechanistic pathways regulated by sirtuins 334
10.3 Functional roles of sirtuins in cancer 337
10.4 Sirtuins in cancer metabolic reprogramming 341
10.5 Therapeutic targeting strategies 345
10.6 Future perspectives in personalized cancer therapy 351
10.7 Conclusion 355
AI disclosure 355
References 356

11. Sirtuins in inflammation and autoimmunity 363
Mirunalini Gobinath, Parikshit Roychowdhury, Sagarika Mukherjee and Mohd Aftab Siddiqui
11.1 Introduction 363
References 382

Part 5 Therapeutic applications

12. Sirtuin modulators: small molecules and natural compounds 393
Rupal Dubey and Pranav Kumar Prabhakar
12.1 Introduction 393
12.2 Enzymatic activity of sirtuins 395
12.3 Small-molecule modulators of sirtuins: an overview 397

12.4 Future perspectives 402
12.5 Conclusion 403
References 404

13. Sirtuin-targeted therapies: current challenges, clinical trials, and future directions 409

Binapani Barik, Lipanjali Badhei and Martin F. Desimone

List of abbreviations 409
13.1 Introduction 410
13.2 Introduction to targeted therapy 411
13.3 Limitations of targeted therapy 411
13.4 Importance of targeting cellular regulators 412
13.5 Sirtuins: model of cellular regulation therapy 414
13.6 Sirtuins 415
13.7 Structure of sirtuin 415
13.8 Member of sirtuin family 416
13.9 General and biological function of sirtuin 417
13.10 Targeted therapies 419
13.11 Drawbacks of conventional drug therapy 420
13.12 Potential of sirtuins as a targeted therapy 421
13.13 Current challenges in sirtuin-targeted therapies 423
13.14 Clinical trials 430
13.15 Future direction 432
13.16 Conclusion 434
References 434

14. Translational perspectives in drug discovery 441

Arpita Robel Khamle, Varshini Dayanand Kore, Abhishek Lakhera, Saroj Kumar Panda, Manish Bhalla and Parth Sarthi Sen Gupta

14.1 Introduction 441
14.2 Sirtuins as therapeutic targets 446

14.3 Translational drug discovery pipeline for sirtuins 449
14.4 Strategies to modulate sirtuin activity 454
14.5 Technological advancements 459
14.6 Challenges and limitations 462
14.7 Translational evaluation of sirtuin modulators 464
14.8 Emerging and future directions 466
14.9 Conclusion 468
References 470

Part 6 Future directions and challenges

15. Emerging trends in sirtuin research 481

Shubhadeep Mondal, Suratna Dass, Raju Samanta, Biplab Debnath, Mohini Mondal and Bimlesh Kumar

15.1 Introduction 481
15.2 The sirtuin family: structure and isoforms 485
15.3 Sirtuins and their role in cellular homeostasis 489
15.4 Sirtuins in DNA repair and genome stability 492
15.5 Mitochondrial function and sirtuins 496
15.6 Sirtuins in immune response modulation 498
15.7 Advancements in sirtuin substrate discovery 502
15.8 Sirtuin modulation and therapeutic potential 506
15.9 Isoform-specificity and clinical implications 511
15.10 Ongoing controversies and future directions 514
15.11 Conclusion 519
References 521

16. Technological advancements in sirtuin analysis 529

Amlan Bishal, Nabanita Manna, Bratati Pakhira, Sudeshna Khanra and Debjita Sett

16.1 Introduction 529
16.2 Conventional methods for sirtuin analysis 532

16.3 High-throughput screening techniques 535
16.4 Structural and biophysical analysis 537
16.5 Omics-based approaches 540
16.6 Advanced imaging and live-cell analysis 543
16.7 Computational and systems biology tools 546
16.8 Emerging nanotechnology and microfluidic platforms 548
16.9 Challenges, limitations, and future directions 551
16.10 Conclusion 552
Acknowledgements 552
Credit author statement 552
Conflict of interest 553
Ethical statement 553
References 553

17. Experimental tools for sirtuin modulation: from CRISPR to chemical biology 563

Vijay Singh, Aniruddha Sen, Biplab Debnath, Radheshyam Pal and Mohini Mondal

17.1 Introduction 563
17.2 Molecular basis of sirtuin function 564
17.3 Genetic tools for sirtuin modulation 568
17.4 High-throughput screening for modulators 569
17.5 Biochemical and biophysical assays 574
17.6 Synthetic biology and protein engineering tool 575
17.7 Metabolic engineering and cofactor modulation 576
17.8 Translational applications 580
17.9 Challenges and future directions 583
17.10 Conclusion 586
References 588

18. Ethical and clinical implications of sirtuin therapies 597

Meenakshi Attri, Mohit Agrawal, Asha Raghav, Samiksha Mishra, Hema Chaudhary, Manmohan Singhal and Narender Yadav

18.1 Introduction 597

18.2 Clinical considerations 598

18.3 Ethical implications 603

18.4 Regulatory and policy considerations 605

18.5 Future perspective 606

References 607

Author index 611

Subject index 631

10

The role of sirtuins in cancer progression

Anas Islam[1], Usama Ahmad[1], Mohd Muazzam Khan[1], Talib Hussain[2]

[1]FACULTY OF PHARMACY, INTEGRAL UNIVERSITY, LUCKNOW, UTTAR PRADESH, INDIA [2]DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, COLLEGE OF PHARMACY, UNIVERSITY OF HA'IL, HA'IL, HA'IL, SAUDI ARABIA

10.1 Introduction

Sirtuins represent a highly conserved family of nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases that have emerged as pivotal regulators at the intersection of cellular metabolism, epigenetic regulation, and cancer biology. First identified as the mammalian orthologs of yeast Silent Information Regulator 2 (Sir2), the seven mammalian sirtuins (SIRT1–SIRT7) share a conserved catalytic core domain of approximately 275 amino acids yet exhibit remarkable functional diversity through distinct subcellular localizations, enzymatic activities, and substrate specificities. This evolutionary conservation from bacteria to mammals highlights their fundamental importance in cellular homeostasis and organismal survival. In the context of cancer, sirtuins have garnered substantial attention over the past two decades not merely as metabolic sensors, but as master regulators whose dysregulation profoundly influences tumor initiation, progression, and therapeutic response (Chang & Guarente, 2014; Hong & Lin, 2021; Sanders et al., 2010; Sun & Dang, 2020; Wang et al., 2020; Yu et al., 2024). The structural organization and subcellular compartmentalization of sirtuins confer their functional specialization. SIRT1, SIRT6, and SIRT7 predominantly localize to the nucleus, where they orchestrate chromatin remodeling and gene transcription regulation through histone deacetylation (Chang & Guarente, 2014). SIRT1, the most extensively studied family member, shuttles dynamically between the nucleus and cytoplasm in response to specific cellular stimuli, enabling it to coordinate diverse biological processes ranging from DNA damage repair to metabolic adaptation (Hashemi et al., 2025). SIRT2 functions primarily in the cytosol but translocates to the nucleus during the G2/M phase of the cell cycle to deacetylate histone H4 at lysine 16 (H4K16ac), thereby influencing mitotic progression and genomic stability. The mitochondrial sirtuins—SIRT3, SIRT4, and SIRT5—constitute the largest subgroup and serve as critical guardians of mitochondrial metabolic homeostasis, regulating oxidative phosphorylation (OXPHOS), reactive oxygen species (ROS) production, and nutrient catabolism. SIRT7 resides predominantly in the nucleolus, where it regulates ribosomal RNA transcription through H3K18 deacetylation, thereby controlling protein synthesis and cellular growth (Hamaidi & Kim, 2022; Min and Gao, 2019; Sun & Dang, 2020; Wang et al., 2021).

Unlocking Sirtuins. DOI: https://doi.org/10.1016/B978-0-443-45380-9.00012-2
© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.